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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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P 1647-1547

DUREEN H HOGLE

1647-1106

EXAMINER

HAMILTON BROOK SMITH & REYNOLDS PC

WEIGERT, S

TWO MILITIA DRIVE

ART UNIT

PAPER NUMBER

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DATE MAILED:

11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/018,194	GILCHREST ET AL.
Examiner	Art Unit	
Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 23 August 2001.
- 2a) This action is **FINAL**.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-52 is/are pending in the application.
- 4a) Of the above claim(s) 1-5 and 11-52 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 6-10 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) 1-52 are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                       | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s) _____.  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                              | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6,8,9,13</u> | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION*****Status of Application, Amendments, and/or Claims***

The Information Disclosure Statement received 10/26/01 has been entered into the record. The Information Disclosure Statement received 11/9/99 (Paper 8) has been entered. The Supplemental Information Disclosure Statement received 11/30/00 (Paper 9) has been entered into the record. The Information Disclosure Statement received 8/16/01 (Paper 13) has been entered into the record. Applicant's election of Invention II, (claims 6-10) in Paper No. 14 is acknowledged. In addition, Applicant elected the following Group: SEQ ID NO: 9. It should be noted that claims will be examined insofar as they read on the elected Invention. Claims 1-5 and 11-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Applicant elected Invention II with traverse. The traversal is on the ground(s) that the Invention of preventing keratinocyte cell death in a vertebrate is the same as the Invention of treating Alopecia, because the same ligands are used and presumably the Inventions share the same cell targets. Applicant's arguments are not persuasive, however, since Inventive Groups II and VIII in question were properly restricted as the methods are practiced with materially different process steps for materially different purposes and each method requires a non-coextensive search because of different starting materials, process steps, goals and measured endpoints. The method of group VIII requires human patients with Alopecia Areata, while the method of group II does not. Therefore, the search of the art for the method practiced with the disease of group VIII is different from the search for the methods of Invention II. In addition, since a complete search of

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the art includes a search of the art that renders an invention obvious as well as anticipatory, the additional searches required for examination of Invention II *with* Invention VIII would be extensive, thus presenting an undue burden for the examiner. For the same reasons Applicant's arguments are not persuasive as far as joining Inventions I, V and VI: Rescuing damaged melanocytes from apoptosis is not necessarily the same as inducing skin color; it is done for different purposes and with different measured results. Likewise, methods of inducing hair color and maintaining hair color (Groups III and IV) serve different patient populations, for example. In addition, Applicant traversed the second restriction in which it was required that he/she elect a peptide ligand. The Applicant argued that all three sequences should be examined together. Applicant is reminded that the "KGA" peptide will be searched along with SEQ ID NO: 9; therefore, there are *four* sequences that need be searched. However, the sequences are independent and distinct products having characteristic differences in structure and function and having different uses. A complete search of the art for each sequence, as well as full database searches constitute undue burden if all sequences are searched together.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6-10 are under examination in the Instant Application.

### ***Informalities***

### ***Specification***

The disclosure is objected to because of the following informalities:

***Title***

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "INHIBITION OF APOPTOSIS IN KERATINOCYTES BY A LIGAND OF p75 NERVE GROWTH FACTOR RECEPTOR".

Appropriate correction is required.

**Claim Objections/Rejections**

Claims 8 and 10 are objected to because they recite or encompass non-elected inventions.

Appropriate correction is required.

**Claim Rejections - 35 USC § 112, second paragraph-indefiniteness.**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

**The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the phrase "the pseudo-ligand". There is insufficient antecedent basis for use of the term without defining it in a previous claim. Likewise, the term "pseudo-pseudo-

ligand` is undefined, and in fact, it is difficult to discern the difference between the terms "pseudo-ligand" and "pseudo-pseudo-ligand" in the claim.

***35 USC § 112, first paragraph - lack of enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

**The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 6-10 are rejected under 35 U.S.C. 112, first paragraph, because the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for the limitations of the claims wherein apoptosis is prevented in epidermal keratinocytes as a method of causing hair growth.

Claims 6-10 read on a method of preventing apoptosis in keratinocytes, thereby allowing continuing function of keratinocytes, including presumably those that make hair in the dermal follicle. The claimed ligands to be used for the method of the invention are SEQ ID NO: 9 and the "KGA" fragment of SEQ ID NO: 9.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

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The specification discloses the use of ultraviolet light to cause apoptosis of cultured keratinocytes and describes experiments in which NGF enhances cultured keratinocyte survival after UV irradiation. The specification also describes correlations between BCL-2 levels and NGF concentrations bathing the cells, thus implying an apoptotic mechanism for keratinocyte cell death caused by UV irradiation. Two ligands for the p75 NGF receptor are disclosed: the cyclic decapeptide CATDIKGAE<sup>C</sup>- SEQ ID NO: 9- and the "KGA" fragment of SEQ ID NO: 9. Both peptides are high affinity ligands for p75, binding at nanomole/liter concentrations (US PAT: 6,242,416, Gilchrest, et al, Fig. 1; Yaar, M, et al, J. Invest. Dermatol. **108**:568a).

However, the claims read on a method of inducing hair growth in the epidermis by inhibiting apoptosis in keratinocytes. The ligands recited to be used in the method are the cyclic decapeptide CATDIKGAE<sup>C</sup> and the "KGA" fragment of the peptide. There is no enabling discussion or working examples disclosed in the instant application as to how to practice the method of inhibiting hair loss in the epidermis of a *vertebrate or mammal*. In addition, hair loss in mammals is caused by a variety of interacting factors, many of them not well understood (Ben-Ari, Bioscience, **50**: 303). It probably involves several types of cells in addition to keratinocytes, as well as immune factors and the influences of reproductive and parathyroid or parathyroid-related peptide hormones (Christensen, Science News, **160**, 254, 2001). There are also different mechanisms of hair loss depending on the area of skin studied. It is clear that apoptosis of *cultured* keratinocytes caused by irradiation with UV light is a poor model of hair loss in a mammal.

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The claims read on a method of inducing hair growth in the epidermis by inhibiting apoptosis in keratinocytes using the ligands: cyclic CATDIKGAE (SEQ ID NO:9) and the "KGA" fragment. However, the ligand disclosed in the specification as used for the method of the invention is Nerve Growth Factor or NGF. There is no reason to infer- because NGF inhibits apoptosis in the damaged cells- that the peptide of SEQ ID NO: 9 and *KGA* will do the same. The peptides of SEQ ID NO: 9 and *KGA* are small fragments of the large  $\beta$ -subunit of NGF, and have been shown to bind p75 (US PAT: 6,242,416, Gilchrest, et al, Fig. 1; Yaar, M, et al, J. Invest. Dermatol. **108**:568a). However, the mechanism of NGF's anti-apoptotic action may involve receptors other than p75, such as TRK-A receptors (Zigmond, (ed), 1999, Fig. 21.6).

Due to the large quantity of experimentation required to determine how to use the disclosed SEQ ID NO: 9 and *KGA* to induce hair growth in a vertebrate, the lack of direction or guidance in the specification regarding the same, the lack of working examples that apply SEQ ID NO: 9 and *KGA* to the skin of a vertebrate, the state of the art showing the complexities of hair loss syndromes, and the breadth of the claims which embrace many types of hair loss syndromes, --undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

### ***Conclusion***

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 8:30 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW

10/30/01

*Elizabeth C. Glenister*